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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/522,365

09/21/2005

Jean-Charles Quirion

QUIRION1

1397

1444 7590 03/18/2008
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EXAMINER

KRISHNAN, GANAPATHY

ART UNIT

PAPER NUMBER

1623

MAIL DATE

DELIVERY MODE

03/18/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,365	QUIRION ET AL.	
	Examiner	Art Unit	
	Ganapathy Krishnan	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 31 January 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's request for reconsideration of the finality of the rejection of the last Office action mailed 10/31/2007, are persuasive, therefore, **the finality of that action is withdrawn**. New grounds of rejections are set forth below.

The After Final amendment filed 1/31/2008 has been received, entered and carefully considered. The following information provided in the amendment affects the instant application:

1. Claims 7-19 have been canceled.
2. Claim 6 has been amended to clarify the language.
3. Remarks drawn to rejections under 35 USC 112, 102 and 103.

Claims 1-6 are pending in the case.

The following rejections of record are withdrawn:

The rejection of claim 6 under 35 USC 112, second paragraph has been overcome by amendment.

The rejection of Claims 1 and 3 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Quirion et al (Tetrahedron Letters, 2001, 42, 5879-5882; document # AE cited in IDS of 1/25/2005) has been overcome in view of applicants arguments. The instant claims are drawn to a sugar that has an oxygen attached to the anomeric carbon of the sugar. The prior art compound does not have an oxygen attached to the anomeric carbon as pointed out by the applicants.

Art Unit: 1623

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marcotte et al (Tetrahedron Letters, 2001, 42, 5879-5882; document # AE cited in IDS of 1/25/2005) in view of Wong et al (Bioorganic & Medicinal Chemistry Letters, 1998, 8, 2333-2338), both of record.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Art Unit: 1623

Marcotte et al teach a C-glycoside (Structure 1, page 5879) that has a CF₂ group and an alkyl chain that is functionalized with an amine group and an acid function. Quirion teaches that structure 1 is a glycoserine or glycothreonine (page 5879, right column, lines 8-9). According to Marcotte replacement of the anomeric oxygen with a gem difluoromethylene group induces differences in the biological functions of compounds of structure 1, which are also hydrolytically stable. Hence, preparation of new derivatives comprising a gemdifluoromethylene group in the place of anomeric oxygen is a promising avenue for the preparation of new glycoconjugate derivatives (page 5879, left column, lines 7-14). However, Marcotte does not teach specifically a sugar derivative as instantly claimed wherein, an amide group is directly attached to the gemdifluoromethylene group and also has an OPG (oxygen of the OH protected).

Wong et al, drawn to C-glycosides, teach sugar derivatives of structural formula 3-8 (page 2334) that are structurally very close to the compound as instantly claimed. The sugar moiety of Wong has an oxygen attached to the anomeric carbon. According to Wong these structures are useful as mimics of sialyl lewis X as inhibitors of E- and P-selectin (page 2333, abstract and first paragraph). However, Wong does not teach a derivative comprising a gemdifluoromethylene group as instantly claimed.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make compounds of structural formula as claimed in instant claims 1-3 since structurally similar compounds are taught in the prior art to have important biological activity.

One of ordinary skill in the art would be motivated to make the compounds and their compositions as instantly claimed since structurally similar compounds comprising the gemdifluoromethylene group directly attached to the anomeric carbon are hydrolytically stable

Art Unit: 1623

(as taught by Marcotte) and the non halogenated analogs show E- and P-selectin binding inhibition, which is important for treatment of inflammation (as taught by Wong). One of ordinary skill in the art would thus be motivated to make compounds as instantly claimed by incorporating the difluoromethylene moiety in the structure of Wong in order to look for derivatives that are good inhibitors of the said selectins which are also hydrolytically stable.

The rejection of Claims 4-6 under 35 U.S.C. 103(a) as being unpatentable over Lerner et al (J. Org. Chem. 1979, 44(19), 3368-3373) in combination with Furstner (Synthesis, 1989, 571-590) is being maintained for reasons of record.

Response to Applicants Arguments

Regarding the rejections under 35 USC 103 applicants have traversed the rejection arguing that:

1. The compounds recited in the instant claims have an oxygen (protected) at the anomeric carbon and also at the same position a CF₂-R1 group. This feature allows the instant sugar to ring open and close like a normal sugar does and also the CF₂-R1 group cannot be cleaved by enzyme. This is different from what is observed with the prior art (Marcotte) sugars.
2. CF₂ is different from CH₂ because the fluorine atom has different properties compared to hydrogen and the only property that is close is their size.
3. With regard to the method of making the compounds of the instant invention. The Reformatsky reaction of BrCF₂CO₂Et applied to good electrophiles like ketone and aldehydes. It was evident to one of skill in the art that a lactone was not a suitable electrophile. In order to

Art Unit: 1623

make this reaction work $\text{BrCF}_2\text{CO}_2\text{Et}$ should be added to the refluxing solvent containing zinc and the lactone added later. The Reformatsky reaction as instantly claimed has not been performed on a lactone before. The reaction works with a 6-membered lactone and not with a 5-membered lactone in the case of a sugar.

4. Wong teaches glycopeptides that have a CH_2 group and not a CF_2 .

Applicants' arguments have been considered but are not found to be persuasive.

It is seen that applicants' compounds have an oxygen attached to the anomeric carbon and also the $\text{CF}_2\text{-R1}$ group on the same carbon. Lerner teaches sugars that are structurally close to the instant compounds and these have an oxygen (protected; page 3369, Scheme I, structure 4) attached to the anomeric carbon. Marcotte teaches that incorporation of a difluoromethylene group on the anomeric carbon is a promising avenue for preparing glycoconjugate derivatives since the said group may induce differences in the biological functions. Even though Marcotte teaches the replacement of the anomeric carbon with a difluoromethylene group one of skill in the art would want to incorporate this group in a sugar having an anomeric oxygen (as taught by Lerner) in order to look for new glycoconjugate derivatives with interesting biological properties.

One of skill in the art knows that fluorine is close in size to hydrogen and is the most electronegative element and that it alters the properties of the compounds in which it is incorporated. Marcotte may have used the $-\text{CF}_2$ to replace oxygen since $-\text{CF}_2$ is an isostere. But one of skill in the art also knows well that the fluorine atom changes the electronic effects (due to its high electronegativity) of the carbon to which it is attached as well the neighboring carbon. This changes the reactivity of the compounds. This fact coupled with its size, which is very close

Art Unit: 1623

to that of hydrogen has been taken advantage of and many useful fluorinated compounds have been synthesized. This is one other reason that one of skill in the art would incorporate the difluoromethylene group on sugars that also have an anomeric oxygen in order to look for other derivatives with interesting biological activities.

Regarding the method of making the compounds as instantly claimed, it may have been evident to one of skill in the art that a lactone may not be a suitable electrophile for reaction with $\text{BrCF}_2\text{CO}_2\text{Et}$ and its reaction with the carbonyl group of the lactone may not be as facile as with $\text{BrCH}_2\text{CO}_2\text{Et}$. Knowing this fact one of skill in the art would not perform the reaction of $\text{BrCF}_2\text{CO}_2\text{Et}$ with the lactone under the same conditions as the classical Reformatsky reaction of $\text{BrCH}_2\text{CO}_2\text{Et}$ with the lactone. One would alter conditions to induce the reaction. It is well within the skill level of the artisan to perform the reaction by altering the reaction conditions like temperature, reaction time, and also manipulate the order of addition of the reagents, etc., in order to make the reaction work. These are techniques well known to the artisan to be applied to any reaction for the purpose of optimization of reaction conditions. Also, as taught by Furstner (page 575, right column, last paragraph through page 576, left column) the Reformatsky reaction of α -dihalo esters are influenced by reaction conditions. This teaching of Furstner would prompt one of skill in the art to optimize conditions for the reactivity of $\text{BrCF}_2\text{CO}_2\text{Et}$ with the lactone.

Wong does not teach glycopeptides with a CF_2 group. But since fluorine atom is close in size to hydrogen and replacement of hydrogen by fluorine also alters the reactivity one of skill in the art would want to replace the CH_2 group as taught by Wong with a CF_2 in order to look for derivatives with interesting biological activity. Even though they lack an anomeric oxygen the compounds of Wong are structurally close to the ones instantly claimed.

Conclusion

Claims 1-6 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GK

/Shaojia Anna Jiang, Ph.D./

Supervisory Patent Examiner, Art Unit 1623